A computerized system for detecting signals due to drug–drug interactions in spontaneous reporting systems

Yifeng Qian,¹ Xiaofei Ye,¹ Wenmin Du,² Jingtian Ren,³ Yalin Sun,¹ Hainan Wang,^{1,4} Baozhang Luo,¹ Qingbin Gao,¹ Meijing Wu¹ & Jia He¹

¹Department of Health Statistics, Second Military Medical University and ²Adverse Drug Reaction Monitoring Centre of Shanghai, Shanghai, ³Centre for drug re-evaluation, SFDA national centre for ADR Monitoring and ⁴Centre for Drug Evaluation, State Food and Drug Administration, Beijing, China

WHAT IS ALREADY KNOWN ABOUT THE SUBJECT

- Concomitant use of different drugs may yield excessive risk for adverse drug reactions and it is a challenging task to do surveillance on the safety profile of the interaction between different drugs.
- Currently, several methods are used by pharmacoepidemiologists and statisticians to detect possible drug–drug interactions in spontaneous reporting systems.
- However, with the increasing number of reports in the system, there is a growing need for a computerized system that could facilitate the process of data arrangement and detection of drug interaction.

WHAT THIS STUDY ADDS

- We had already developed a computerized system to detect adverse drug reaction signals due to single drugs.
- After the development of this system, interaction between different drugs could also be detected automatically and intelligently.

Correspondence

Professor Jia He, Department of Health Statistics, Second Military Medical University, Shanghai 200433, China.
Tel: +86 21 8187 1441
Fax: +86 21 8187 1441
E-mail: hejia63@yahoo.com

Y.Q., X.Y., W.D and J.R. contributed equally to this work.

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AIMS

In spontaneous reporting systems (SRS), there is a growing need for the automated detection of adverse drug reactions (ADRs) resulting from drug–drug interactions. In addition, special attention is also needed for systems facilitating automated data preprocessing. In our study, we set up a computerized system to signal possible drug–drug interactions by which data acquisition and signal detection could be carried out automatically and the process of data preprocessing could also be facilitated.

METHODS

This system was developed with Microsoft Visual Basic 6.0 and Microsoft Access was used as the database. Crude ADR reports submitted to Shanghai SRS from January 2007 to December 2008 were included in this study. The logistic regression method, the Ω shrinkage measure method, an additive model and a multiplicative model were used for automatic detection of drug–drug interactions where two drugs were used concomitantly.

RESULTS

A total of 33 897 crude ADR reports were acquired from the SRS automatically. The 10 drug combinations most frequently reported were found and the 10 most suspicious drug–drug ADR combinations for each method were detected automatically after the performance of the system.

CONCLUSIONS

Since the detection of drug–drug interaction depends upon the skills and memory of the professionals involved, is time consuming and the number of reports is increasing, this system might be a promising tool for the automated detection of possible drug–drug interactions in SRS.

Introduction

Interaction between drug substances may yield excessive risk for adverse drug reactions (ADR) when two or more drugs are taken in combination. However, in premarketing trials, patients with multiple drug use are usually excluded, which makes the detection of drug–drug interactions in the postmarketing period even more important. The proportion of ADRs due to drug–drug interactions is estimated to be between 6% and 30%, and surveillance on the safety profile of the interaction between different drugs is challenging [1, 2].

Generally, the detection of possible interactions is based on the following concept: when a suspected ADR is reported more frequently in the combination of two drugs compared with the situation where they are used alone, this association might indicate the existence of a drug–drug interaction. The currently used methods for quantitative drug–drug interaction detection include frequentist approaches, regression approaches and Bayesian approaches. The χ^2 test proposed by Alsheikh-Ai and the ADR reporting odds ratios method defined by the Netherlands Pharmacovigilance Foundation Lareb belong to the frequentist approaches [3, 4]. These methods are clear and easy to understand, but this type of approach does not adjust the counts for exposure to the various drug combinations and thus does not provide an appropriate statistical context for studying drug interaction. The logistic regression method presented by van Puijenbroek *et al.* and the log-linear model proposed by DuMouchel are regression approaches [5–7]. These methods offer the possibility of controlling for covariates and tend to achieve more realistic results than the frequentist approaches. The higher order Bayesian confidence propagation neural network method, the interaction signal score method and the Ω shrinkage measure method are Bayesian approaches [8–10]. Bayesian approaches calculate an observed to expected ratio for each relevant drug event or drug–drug event combination in the database and could achieve a more specific result. In addition, an additive model and a multiplicative model have also been presented by which the detected drug interaction signals could be further identified by statistical test [11].

Surveillance schemes based on spontaneous reporting systems (SRS) are a cornerstone of the early detection of drug hazards that are novel by virtue of their clinical nature, severity and/or frequency [12]. The Shanghai ADR SRS is a part of China ADR SRS and one of the major goals of this system is the timely detection of possible new ADRs and interactions. There are 12 000–16 000 ADR reports submitted to the system annually. However, with the increasing number of reports in the system, the setting up of a computerized system that could aid the automated detection of possible drug–drug interactions has become the focus of statisticians and pharmacoepidemiologists. In our study, we set up a computerized system that could

facilitate the process of data acquisition and data arrangement. In addition, the logistic regression method, the Ω shrinkage measure method, the additive model as well as the multiplicative model were carried out automatically for the detection of possible drug interactions. Given the apparent disadvantage of the frequentist approaches, they were not employed in our system. The objective of the present study was to illustrate the computerized system as well as its performance characteristics with the ADR SRS of Shanghai.

Methods

Microsoft visual basic (VB) 6.0 was used as the programming language for this system and Microsoft Access was used as the database. The data were accessed from the database through the structured query language (SQL).

Data acquisition

The data could be downloaded automatically with the system via <http://www.adr.gov.cn>, which was developed by National Adverse Drug Reaction Monitoring Centre of China.

Data coding

The following procedure was used to address the problem of redundant and variable drug nomenclature. The ADR names were coded with World Health Organization (WHO)-Adverse Reaction Terminology using preferred terms, which has been developed for more than 30 years to serve as a basis for rational coding of adverse reaction terms [13]. For example, when dyssomnia was reported as the ADR, then was changed to sleep disorder automatically by the system. In addition, the generic names for drugs were standardized according to catalogue of generic names for common prescription drugs, which was issued by Ministry of Health of China in 2007. The website <http://app1.sfda.gov.cn/datasearch/face3/dir.html> and Chinese Pharmacopoeia were also used as materials for our work [14].

Data pre-processing

When there was only one drug and multiple reactions in a report, then it was broken up into drug–ADR combinations by the system. For the report which included two drugs and multiple reactions, the system broke them up into drug–drug–ADR combinations after this procedure. Reports which included more than two drugs were excluded from the study. As a result, we were able to detect possible drug–drug interactions.

Data inquiry

According to the conditions input in the system, the data could be accessed from the database through SQL.

Signal detection

The development and use of data mining tools for detecting new safety signals in postmarketing spontaneous reporting databases is becoming prevalent among regulators and drug monitoring centres as well as pharmaceutical companies, with hopes for earlier and more efficient detection of new safety signals postmarketing [15]. The logistic regression method has been applied by the Netherlands Pharmacovigilance Foundation Lareb. Before the performance of the method, all records in the database were automatically divided into cases and non-cases by the system according to different ADRs. Cases were defined as patients who reported ADRs of interest, while 'noncases' consisted of all other reports. ADR reporting ORs were first calculated for the comparison of reports where both drug A and drug B were used concomitantly with reports where neither drug A nor drug B was used [4]. Then the ADR reporting ORs were adjusted for age and gender and calculated by logistic regression. In constructing the logistic model, drug A, drug B as well as the concomitant use of A and B were coded, respectively, by the system according to different ADRs and the model would then look like:

$$\log(\text{odds}) = \beta_0 + \beta_2 a + \beta_3 G + \beta_4 A + \beta_5 B + \beta_6 AB$$

where a = age, G = gender, A = drug A, B = drug B, AB = the concomitant use of A and B.

The Ω shrinkage measure method has also been carried out for detecting suspicious drug–drug combinations with the entire WHO database. After the prior and posterior distribution for μ is assumed to be gamma-distributed, the exact credibility interval limits for μ can be found numerically as solutions to the following equation:

$$\int_0^{\mu_q} \frac{(E_{111} + \alpha)^{n_{111} + \alpha}}{\Gamma(n_{111} + \alpha)} u^{n_{111} + \alpha - 1} e^{-(n_{111} + \alpha)u} du = q$$

Norén *et al.* have given a detailed description of the computation of the Ω shrinkage measure method and a signal is considered to be generated when $\Omega_{0.25} > 0$ [10].

The additive and multiplicative models have also been applied in the Food and Drug Administration's (FDA) database for the detection drug interaction. When performing the multiplicative model, it was assumed that the risk associated with a drug multiplies with the background risk and the performance of the additive model was under the assumption that the risk associated with a drug adds to the background risk. $RRAB/(RRA \times RRB) > 1$ and $RDAB - RDA + RDB > 0$, respectively, indicate that a drug interaction signal is generated by the multiplicative and the additive model when the corresponding P -value is also < 0.05 . The theory of the two models was elaborated by Thakrar *et al.* and we refer to the formulae in their work [11].

Table 1

The 10 drug combinations that were reported most in the database

Drug A	Drug B	Report number
Cefuroxime	Sodium chloride	76
Interferon alfa-2a	Ribavirin	62
Levofloxacin hydrochloride	Sodium chloride	59
Penicillin sodium	Sodium chloride	56
Penicillin sodium	Piperaxillin	53
Clindamycin	Sodium chloride	48
Piperaxillin	Sodium chloride	47
Cefuroxime	Ribavirin	45
Azlocillin	Penicillin sodium	35
Capecitabine	Oxaliplatin	35

Results

All in all, 33 897 crude ADR reports from January 2007 to December 2008 were acquired from the SRS automatically, 5345 (15.76%) of which were detected with two drugs. The number of drug combinations involved in the database was 2664, 70 of which were reported as > 10 . The top 10 drug combinations were detected and listed in Table 1.

According to the results in Table 1, a well-known example of interaction between interferon alfa-2a and ribavirin, which could increase the incidence rate of anaemia, was selected by us to check whether it could be detected by our system. Results showed that the system detected the established drug–drug interaction as desired (Table 2).

With the system we carried out a database-wide screen. Tables 3–5 show the 10 most suspicious drug–drug–ADR combinations detected by the three methods, respectively. The P -values for the interaction term of AB in the logistic model for all 10 combinations were < 0.05 . All results in Table 5 were first detected by the additive model and then validated by the multiplicative model. Different methods were also compared according to the detected combinations during the database-wide screen in Table 6.

Discussion

A major function of the SRS is generating new signals [16]. For this purpose, all reports are individually reviewed and detection depends upon the skills and memory of the professionals involved. Since this procedure is time consuming and the number of reports is increasing, there is a growing need for an automated system that could facilitate the process of data arrangement and detection of ADR, especially in some special cases such as drug–drug interactions. We had already developed a computerized system to detect ADR signals due to single drugs [17]. In this study, with the use of MS VB 6.0 and MS Access, we present another computerized system in which data acquisition

Table 2
Results for the established drug–drug interaction

Algorithm	Variable	<i>n</i>	Value
Ω shrinkage measure	Ω_{025}	5	1.23
Logistic regression	OR (interferon alfa-2a)	1	13.16 (1.65–91.95)
	OR (ribavirin)	0	0 (0– ∞)
	OR (drug combination)	5	129.68 (45.45–334.85)
The additive model	δ	5	0.07
The multiplicative model	δ	5	*

n, the number of the combinations when both of the drugs were used concomitantly and a certain adverse drug reaction was caused as a result. The *P*-value for the interaction term of AB in the logistic model was <0.001. The *P*-value for the additive and multiplicative model was 0.021 and <0.001, respectively. * RRA × RRB was 0 and the δ could not be calculated as a result.

Table 3
The 10 most suspicious drug–drug–adverse drug reaction (ADR) combinations detected by logistic regression in the database-wide screen

Drug combinations (A and B)		ADR	<i>n</i>	OR (drug A)	OR (drug B)	OR (A and B)
Levodopa and benserazide	Amantadine	Ataxia	4	117.66 (30.04–460.91)	0 (0– ∞)	>999.99 (>999.99–>999.99)
Interferon alfa-2a	Ribavirin	Thyroid disorder	21	769.16 (317.54–>999.99)	0 (0– ∞)	>999.99 (898.54–>999.99)
Mycophenolate mofetil	Prednisone	Abnormal lung function	6	114.77 (32.23–408.68)	0 (0– ∞)	>999.99 (491.66–>999.99)
Chlorpromazine	Risperidone	Extrapyramidal disorder	5	200.62 (125.72–320.15)	202.48 (137.27–298.65)	904.65 (172.24–>999.99)
Glucophage	Gliclazide	Hypoglycaemia	3	5.63 (0.76–41.45)	0 (0– ∞)	647.83 (101.91–>999.99)
Mycophenolate mofetil	Ciclosporin	Constipation	4	0 (0– ∞)	0 (0– ∞)	257.25 (62.71–>999.99)
Interferon alfa-2a	Ribavirin	Marrow suppression	33	53.30 (34.57–82.20)	0 (0– ∞)	156.95 (93.41–263.72)
Azithromycin	Floxacin	Sleep disorder	5	0.32 (0.08–1.27)	11.56 (7.16–18.67)	87.93 (30.77–251.27)
Capecitabine	Oxaliplatin	Thrombocytopenia	4	0 (0– ∞)	0 (0– ∞)	45.03 (15.34–132.19)
Mezlocillin	Penicillin sodium	Allergic reaction	7	0.76 (0.28–2.08)	1.88 (1.46–2.41)	4.33 (1.86–10.05)

Table 4
The 10 most suspicious drug–drug–adverse drug reaction (ADR) combinations detected by the Ω shrinkage measure method

Drug combinations (A and B)		ADR	<i>n</i>	Ω_{025}
Mycophenolate mofetil	Ciclosporin	Constipation	4	1.69
Capecitabine	Oxaliplatin	Thrombocytopenia	4	1.56
Levodopa and benserazide	Benzhexol	Neurosis	6	1.50
Methotrexate	Dexamethasone	Muscle weakness	7	1.34
Levodopa and benserazide	Amantadine	Ataxia	4	1.18
Mycophenolate mofetil	Prednisone	Abnormal lung function	6	0.80
Glucophage	Gliclazide	Hypoglycaemia	3	0.66
Interferon alfa-2a	Ribavirin	Thyroid disorder	21	0.74
Tarceva	Gemcitabine	Diarrhoea	5	0.50
Azithromycin	Floxacin	Sleep disorder	5	0.42

could be carried out automatically and the process of data preprocessing could be facilitated. Moreover, after the database-wide screen, 10 drug–drug–ADR combinations with the highest statistical scores for each method were detected, which could be submitted to an expert panel to make a decision. The results indicate that this system could help to download data automatically and detect drug interactions intelligently.

The analysis of possible drug–drug interactions is based on the concept that a suspected ADR is more often reported on the combination of two drugs compared with the situation where either of these drugs has been used in absence of the other [18]. The advantage of logistic regression is that it offers the possibility for controlling for covariates, and furthermore offers a possibility of analysing the use of interaction terms in more detail. However, the use of

Table 5

The 10 most suspicious drug–drug–adverse drug reaction (ADR) combinations detected by the additive and multiplicative model

Drug combinations (A and B)		Adverse drug reaction	<i>n</i>	δ_1	P_1	δ_2	P_2
Levodopa and benserazide	Amantadine	Ataxia	4	0.8	<0.001	*	<0.001
Levodopa and benserazide	Benzhexol	Neurosis	6	0.78	<0.001	*	<0.001
Tarceva	Gemcitabine	Diarrhoea	5	0.66	<0.001	6.91	<0.001
Mycophenolate mofetil	Ciclosporin	Constipation	4	0.5	0.005	*	<0.001
Interferon alfa-2a	Ribavirin	Marrow suppression	33	0.27	<0.001	3.52	<0.001
Interferon alfa-2a	Ribavirin	Thyroid disorder	21	0.21	<0.001	*	<0.001
Azithromycin	Fleroxacin	Sleep disorder	5	0.21	0.011	21.22	<0.001
Cefuroxime	Clindamycin	Local swelling	4	0.21	0.027	13.44	<0.001
Mezlocillin	Penicillin sodium	Allergic reaction	7	0.15	0.029	3.98	<0.001
Interferon alfa-2a	Ribavirin	Leucopenia	17	0.12	<0.001	1.67	<0.001

δ_1 and P_1 represent the result of the additive model and δ_2 and P_2 represent the result of the multiplicative model. The meaning of * is as in Table 2.

Table 6

Comparison of different methods according to the detected combinations during the database-wide screen

Drug combinations (A and B)		Adverse drug reaction	<i>n</i>	Signal detection methods		
				Method A*	Method B†	Method C‡
Mycophenolate mofetil	Ciclosporin	Constipation	4	+	+	+
Azithromycin	Fleroxacin	Sleep disorder	5	+	+	+
Levodopa and benserazide	Amantadine	Ataxia	4	+	+	+
Interferon alfa-2a	Ribavirin	Thyroid disorder	21	+	+	+
Mycophenolate mofetil	Prednisone	Abnormal lung function	6	+	+	–
Glucophage	Gliclazide	Hypoglycaemia	3	+	+	–
Capecitabine	Oxaliplatin	Thrombocytopenia	4	+	+	–
Chlorpromazine	Risperidone	Extrapyramidal disorder	5	+	–	–
Interferon alfa-2a	Ribavirin	Marrow suppression	33	+	–	+
Mezlocillin	Penicillin sodium	Allergic reaction	7	+	–	+
Tarceva	Gemcitabine	Diarrhoea	5	–	+	+
Levodopa and benserazide	Benzhexol	Neurosis	6	–	+	+
Methotrexate	Dexamethasone	Muscle weakness	7	–	+	–
Cefuroxime	Clindamycin	Local swelling	4	–	–	+
Interferon alfa-2a	Ribavirin	Leucopenia	17	–	–	+

*Method A: the logistic regression method.; †Method B: the Ω shrinkage measure method. ‡Method C: the additive and multiplicative model; +, the combination was detected by the method; –, the combination was not detected by the method.

the method for the assessment of interaction has been criticized by some epidemiologists, who believe that such models are not suitable for detecting drug interactions [19–21]. Norén *et al.* have also argued that logistic regression is prone to miss some reporting patterns strongly suggestive of suspected drug–drug interaction and have proposed the alternative Ω shrinkage measure method. After a confirmatory study using the WHO database, they believe that the Ω shrinkage measure is a more sophisticated method [10]. The presentation of the multiplicative and additive model provides another way to analyse possible interactions between two drugs. The characteristic of the two models is that the detected signal could be further validated by statistical tests. After their application with FDA's database, the additive model is found to be more sensitive in detecting interaction signals and the multiplicative model may further help qualify the strength of the

signal detected by the additive model [11]. In fact, there has been a paucity of studies comparing the performance of different methods. According to our results listed in Table 6, seven combinations were detected by two methods and four combinations were even detected by all three methods, which may reflect the fact that the three methods are highly correlated. However, there was no gold standard for algorithms dealing with signal detection; as a result, problems such as sensitivity and specificity as well as the false positivity and false negativity of the three methods were not further researched in our study [22–24].

In view of the fact that large collections of individual case safety reports clearly constitute very complex sources of information, the results were also considered from the pharmacology perspective to determine whether there was interaction between the detected drug combinations. We found it pharmacologically plausible that most of

the drug combinations interacted with each other. For example, it has been reported that the combined use of interferon alfa-2a and ribavirin could lead to the onset of thyroid disorder and marrow suppression [25]. Much clinical practice has also shown that capecitabine and oxaliplatin will increase the incidence rate of thrombocytopenia when they are used concomitantly [26, 27]. However, as regards drug combinations such as azithromycin and fleroxacin, we found no evidence to suggest that sleep disorder will be caused by the concomitant use of the two drugs. As a result, we believe that such combinations should be sent to the pharmacologist for further validation to determine to what extent the highlighted results are worthy of further follow-up or just driven by underlying data quality issues.

The detection of drug–drug interactions is much more complicated than the detection of drug–event combinations because of the relatively lower incidence rates and background reporting rates in SRS. Consequently, although much effort has been devoted to developing methods for detecting possible drug interactions, there are still no reports in the literature suggesting that any of the proposed interaction detection methods have been implemented for routine ADR surveillance. Nor are we aware of any examples of early warnings on drug–drug interaction produced by any of the methods. However, quantitative methods are undoubtedly indispensable for large collections of SRS data. In our research, all three methods were validated by case studies in the database and detected possible drug interaction signals. We will employ these methods for routine surveillance in our database for further analysis in our future research.

The selection of Ms Access as the database is mainly because of its availability and ease of use. However, with the increasing number of ADR reports, SQL Server 2000, which is more powerful for dealing with large databases, will be selected to replace MS Access. The aim of this study was to describe the development of a system that could aid the process of signal detection and promote the application of currently developed methods. Different methods employed by the system will be compared in more detail after their application with different databases. In addition, the employment of more sophisticated methods for interaction detection will also be the focus of our future work.

Conclusion

In SRS, there is a growing need for automatic detection of drug–drug interaction. In our study, we have developed a computerized system that could facilitate data arrangement and the process of signal detection. In addition, a database-wide screen was carried out to signal possible drug interactions with three different methods. After its application in the Shanghai ADR SRS, the system

described promises to be a useful tool in analysing possible interactions.

Competing interests

None to declare.

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